Progress Report: March 27, 1996

Title: Noise-tolerant Neural Networks Controlling Adaptive Behavior in Autonomous Agents

Grant No: N00014-94-1-0642

PI: Shawn R. Lockery

The lab has grown significantly in the past year. Two postdoctoral fellows mentioned in the previous Progress Report are now in house and fully up to speed. One is working on the physiological aspects of the project (Specific Aim 2); the other is working on the modeling (Specific Aim 3). I am also pleased to report that I now have a graduate student. He is working exclusively on the behavioral analysis of nematode chemotaxis. I now have, therefore, implemented my original plan for the lab: to investigate chemotaxis at the behavioral, physiological, and theoretical levels simultaneously and interactively. I have also hired a half-time technician to help with the physiology.

As a result of this increase in personnel and several breakthroughs they have made, substantial progress has been achieved on 4 of the 5 Specific Aims of this project. These are discussed in turn below.

Specific Aims and Progress

(1) To determine the sequence and time-dependence of motor commands for chemotaxis using high resolution measurements of the behavior of *C. elegans* in chemical gradients.

We used video tape analysis of nematodes chemotaxing in large arenas to determine which of several previously identified behavioral strategies nematodes actually employ. We showed that the frequency of sudden turning events, which reorient the animal, is not related to the chemical concentration. This rules out klinokinesis as an important mechanism in *C. elegans* and suggests nematodes modulate forward velocity (orthokinesis) or turning angle (klinotaxis).

To determine with of these two strategies nematodes use, we have identified and purchased an automated tracking system that will allow us to locate the nematode at high magnification at any position in a wide arena, and to reconstruct nematode tracks in time and space.

(2) To determine the fundamental operating principles of the *C. elegans* chemoreceptors, neurons, muscles, and synapses using newly developed electrophysiological techniques.

We have improved the experimental success rate by a factor of ten. This has been the result of major changes at all levels of the procedure including (1) finding a new glue for restraining the nematodes that is less toxic, (2) inventing a new gluing procedure that is faster and more reliable, (3) developing a method of getting homogeneous populations of nematodes, (4) developing new

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11 Jul 97

From: Director, Office of Naval Research, Seattle Regional Office, 1107 NE 45th St., Suite 350, Seattle, WA 98105
To: Defense Technical Center, Attn: P. Mawby, 8725 John J. Kingman Rd., Suite 0944, Ft. Belvoir, VA 22060-6218

Subj: RETURNED GRANTEE/CONTRACTOR TECHNICAL REPORTS

1. This confirms our conversations of 27 Feb 97 and 11 Jul 97. Enclosed are a number of technical reports which were returned to our agency for lack of clear distribution availability statement. This confirms that all reports are unclassified and are "APPROVED FOR PUBLIC RELEASE" with no restrictions.

2. Please contact me if you require additional information. My e-mail is *silverr@onr.navy.mil* and my phone is (206) 625-3196.

ROBERT J. SILVERMAN

UNIVERSITY OF OREGON

April 1, 1996

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RE: Progress Report for Grant #N00014-94-1-0642, Shawn R. Lockery

To the Director:

Dr. Shawn R. Lockery has made a few changes to the progress report for the above referenced grant entitled "Noise-Tolerant Neural Networks Controlling Adaptive Behavior in Autonomous Agents." He asked me to send the revised copy to you to replace the one that was sent to you last week.

Thank you.

Sincerely,

Pat Edwards

Pat Edwards
Grants Coordinator

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physiological salines, (5) finding a new method for breaking into cells to form the whole-cell patch configuration, and (6) changing the pipette tip shape.

In the previous Progress Report, I reported we had made cell-attached patch clamp recordings from *C. elegans* neurons labeled transgenically with Green Fluorescent Protein (GFP). In a second methodological development, we have now taken the critical next step of showing it is possible to make whole-cell patch clamp recordings as well. Recordings from these neurons were identical to recordings from unlabeled neurons. This shows that the presence of GFP does not disrupt the biophysical functions of the cell, even after illumination with intense blue light to excite the fluorescence. This is an important result because it means we can now record membrane potential and voltage dependent current from neurons whose identity is known unambiguously.

We have used these new techniques to begin to define the basic operating principles of the *C. elegans* nervous system for the first time. The main result is a fundamental one: we have found that *C. elegans* neurons are dominated by outward (hyperpolarizing) voltage dependent currents and that *C. elegans* neurons do not exhibit classical, all-or-none, action potentials. This finding is consistent with previous results from *Ascaris suum*, a larger species of nematode that is easier to record from. It suggests that signal propagation in *C. elegans* neurons is largely passive and greatly simplifies the project of building large-scale models of *C. elegans* neural networks, especially the large network controlling chemotaxis, since it is not necessary to include the voltage-dependent ionic conductances underlying the action potential. We also find that the time constant of *C. elegans* neurons is very small with respect to the time scale of chemotaxis behavior. This means the chemotaxis network is probably at or near steady-state activity levels at all times. This finding will greatly facilitate the robotics project, since the physical plant of the robot is essentially a steady-state element.

(3) To construct and analyze a realistic computer model of the *C. elegans* chemotaxis control circuitry that reproduces the motor control commands inferred from analysis of the behavior.

We have constructed network models of the chemotaxis network that successfully guide a simulated nematode up a chemical concentration gradient. Neurons in the models are represented realistically as single compartment neurons. This representation is consistent with physiological estimates of membrane resistivity in *C. elegans* neurons. Connections in the model were determined using simulated annealing, a neural network optimization technique. The cost function in the annealing was the integral of time x distance from the center of the gradient. Although the biological network contains 40 neurons, we have found that six neurons, and in some cases just three, are sufficient for the behavior. Moreover, the networks can be optimized in a short time (tens of minutes) and there are many different solutions (sets of connection strengths) that solve the chemotaxis problem. We have shown, for example, that the side-to-side movements of the head, long thought to be necessary for chemotaxis in nematodes, are not necessary. The fact that the models can be easily optimized is a major achievement, since we could not be certain that a solution exists for the problem as we have cast it. Moreover, it

suggests that it will be even easier to construct a realistic model of all 40 neurons in the biological network, one of the major goals of this project.

(4) To determine the self-adaptive mechanisms whereby target preference is altered as the animal learns new relationships between food and chemical stimuli.

No progress to date.

(5) To demonstrate the practical utility of the biological algorithm for orientation, and its adaptive mechanisms, by implementing them in an autonomous vehicle capable of moving to targets and altering target preference.

I have recruited a rotation student with a combined background in neurobiology and computer science to begin this project. He will start 1 April, 1996. His main task will be to determine whether the model chemotaxis networks found using simulated annealing can be used to control a chemotaxing robot in the real world.

Publications

Papers in preparation

Last year I reported that the paper describing the physiology was in preparation for submission to *Science*. After consulting with senior colleagues, including one who is and editor for *Science*, I have decided to withhold the paper until the summer, when we expect to have a stronger biological result in hand.

A paper on the modeling work is in preparation for submission to *Neural Information Processing Systems*, and for submission to *Computational Neuroscience*.

Related publications

Kristan, W.B., Jr, Lockery S.R., and Lewis, J.E. (1995) Using reflexive behaviors of the medicinal leech to study information processing. *J. Neurobiol.*, **27**:380-9.

Davis, M.W., Somerville, D., Lee, R.Y.N., Lockery, S., Avery, L., and Fambrough, D.M. (1995) Mutations in the *Caenorhabditis elegans* Na, K-ATPase alph-subunit gene, *eat-6*, disrupt excitable cell function. *J. Neurosci.* **15**:8408-8418.

Avery, L., Raizen, D., and Lockery, S.R. (1995) Electrophysiological Methods. In Epstein, H.F. and Shakes, D.C. (eds.) *C. elegans*: *Modern Biological Analysis of an Organism*. Academic Press, Orlando. pp. 251-269.

Lockery, S.R. (1995) Signal propagation in the nerve ring of the nematode *C. elegans*. *Soc. Neurosci. Abstr.* 569.7 p. Part 2, p. 1454.